P903

Phase 1a Randomized, Double-Blind, Placebo-Controlled, Single-Ascending Dose and Multiple-Ascending Dose Studies of Orally Inhaled GB002 in Healthy Adult Subjects

[1]Jack Li, [1]Mason Yamashita, [1]Matt Cravets, [2]Cynthia Zamora, [1]Ramona McCaffrey, [1]Richard Aranda, [1]Lawrence S. Zisman

[1]Gossamer Bio, Inc., San Diego, CA; [2]Worldwide Clinical Trials, San Antonio, TX

BACKGROUND

- Pulmonary arterial hypertension (PAH) is an orphan disease associated with high morbidity and mortality with high unmet medical needs
- Increased platelet-derived growth factor receptor (PDGFR) signaling plays a role in the pathogenesis of PAH; inhibition of this pathway may improve cardiopulmonary hemodynamics in patients with PAH[1,2]
- GB002 (formerly PK10571) is a potent, small molecule, PDGFR kinase inhibitor in development as an orally inhaled, dry powder formulation to directly target the diseased lung in PAH
- In preclinical rat models, the pharmacokinetic profile of inhaled GB002 was characterized by a rapid decrease in plasma concentrations and high, sustained lung concentrations
- Preclinical efficacy of GB002 has been demonstrated in two animal models of PAH, the rat monocrotaline plus pneumonectomy model and the SUGEN5416 hypoxia model, supported by significant reductions in pulmonary artery systolic pressure compared to vehicle[3,4]

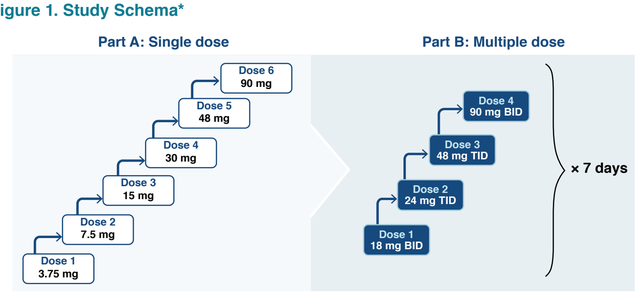
OBJECTIVES

- **Primary**: Determine safety and tolerability of single and multiple doses of GB002 by oral inhalation in healthy adult subjects
- **Secondary**: Evaluate the pharmacokinetics (PK) of GB002 following single- and multiple-dose regimens

METHODS

- Two phase 1a, randomized, double-blind, placebo-controlled studies (**Figure 1**)
  - Study 1 evaluated GB002 in single doses of 3.75 mg, 7.5 mg. 15 mg, 30 mg, and 48 mg and in multiple doses of 18 mg, 24 mg, and 48 mg given twice daily for 7 days
  - Study 2 evaluated GB002 in single doses of 90 mg and in multiple doses of 90 mg given twice daily for 7 days
  - Part A comprised the single ascending dose study, in which subjects received one of six doses of GB002 or placebo
  - Part B comprised the multiple ascending dose study; GB002 doses and schedules were determined by safety and PK data from Part A
- Subjects were healthy, non-smoking adults, 18-55 years of age, body mass index 18-32 kg/m^2
- GB002 or matching placebo powder was delivered by a Plastiape dry powder inhaler
- At each dose, six or seven subjects received active drug (GB002) and two subjects received placebo

Figure 1. Study Schema*



*Represents two studies with the same design. BID, twice daily, TID, three times daily.

- Serial blood and urine samples were collected and analyzed for GB002 with a validated assay for pharmacokinetic (PK) analysis
- Safety assessments included adverse event (AE) reporting, physical exam, clinical laboratories, ECGs, and pulmonary function tests

RESULTS

- GB002 was administered to 62 healthy adult subjects in single doses of 3.75 to 90 mg and multiple doses of 18 to 90 mg twice daily (BID) for 7 days

Table 1. Baseline Demographics

	Single Dose							Multiple Dose				
		GB002							GB002			
	Placebo (n = 12)	3.75 mg (n = 6)	7.5 mg (n = 6)	15 mg (n = 6)	30 mg (n = 6)	48 mg (n = 7)	90 mg (n = 6)	Placebo (n = 8)	18 mg BID (n = 6)	24 mg TID (n = 7)	48 mg TID (n =6)	90 mg BID (n = 6)
Age, years	40.0 (9.0)	39.0 (7.5)	36.8 (10.3)	38.5 (8.8)	39.5 (6.3)	35.4 (9.6)	44.2 (9.9)	33.4 (9.7)	49.3 (4.1)	31.7 (8.8)	41.0 (6.1)	38.7 (6.3)
Male	8 (66.7)	3 (50.0)	3 (50.0)	2 (33.3)	3 (50.0)	4 (57.1)	6 (100)	6 (75.0)	2 (33.3)	4 (57.1)	3 (50.0)	4 (66.7)
Race												
White	10 (83.3)	5 (83.3)	5 (83.3)	5 (83.3)	3 (50.0)	5 (71.4)	5 (83.3)	7 (87.5)	3 (50.0)	5 (71.4)	4 (66.7)	3 (50.0)
Black	2 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	3 (50.0)	2 (28.6)	–	–	3 (50.0)	2 (28.6)	2 (33.3)	3 (50.0)
Asian	–	–	–	–	–	–	–	1 (12.5)	–	–	–	–
American Indian or Alaskan Native	–	–	–	–	–	–	1 (16.7)	–	–	–	–	–
Body Mass Index, kg/m^2	26.9 (2.6)	28.1 (3.2)	23.9 (3.4)	26.6 (1.9)	30.2 (1.5)	25.9 (3.6)	25.7 (4.1)	28.4 (3.0)	28.2 (2.7)	26.9 (3.6)	23.2 (2.6)	27.7 (2.5)

Continuous data are presented as mean (SD); categorical data are presented as n (%).

Pharmacokinetics

- Following single and multiple oral inhalations, GB002 was rapidly absorbed into the systemic circulation; median time to maximum concentration (T_{max}) ranged from 3 to 5 minutes post-dose (**Figures 2 and 3**)
- GB002 plasma concentrations declined rapidly after T_{max}. Mean terminal elimination half-life ranged from 3.1 to 5.8 hours
- GB002 peak plasma concentrations (C_{max}) and area under the concentration-time curves (AUC) increased in an approximately dose-proportional manner following single and multiple dose administrations
- Steady-state plasma levels were reached by Day 3 following multiple doses, with minimal accumulation in plasma after multiple twice daily (BID) or three times daily (TID) dosing
- A negligible amount (< 0.1%) of orally inhaled GB002 was excreted as unchanged GB002 in the urine

Figure 2. Mean GB002 Plasma Concentration vs Time Profiles: 3.75 mg – 90 mg Single Dose

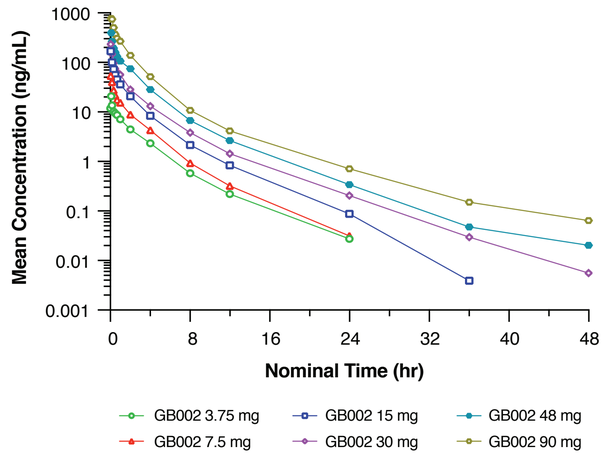
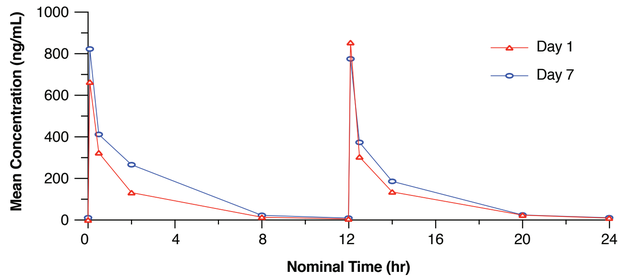


Figure 3. Mean GB002 Plasma Concentration vs Time Profiles, Days 1 and 7: 90 mg Twice Daily × 7 Days



Safety

- The most common adverse events were respiratory-related, primarily throat irritation and cough, which were mild in severity and similar in incidence to placebo
- No serious adverse events were reported
- No reported AE led to study drug discontinuation

CONCLUSIONS

- GB002 is an orally inhaled PDGFR kinase inhibitor designed for targeted delivery to the lungs that is in clinical development for patients with PAH
- Following single and multiple doses, GB002 was rapidly absorbed into and cleared from the systemic circulation
- GB002 exposure increased in an approximately dose-proportional manner following single and multiple dosing administration. Minimal accumulation in plasma was observed after multiple days of BID or TID doses.
- In healthy volunteers, inhalation of GB002 was well tolerated
- These results are consistent with prior data from preclinical models and support the hypothesis that inhaled GB002 will result in effective local lung concentrations while limiting systemic exposure

REFERENCES

1. Hoeper MM, et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. *Circulation.* 2013; 127:1128–1138.
2. Medarametla V, et al. PK10453, a nonselective platelet-derived growth factor receptor inhibitor, prevents the progression of pulmonary arterial hypertension. *Pulm Circ.* 2014; 4: 82–102.
3. Sitapara R, et al. In vivo efficacy of a novel, inhaled PDGFRα/β inhibitor, GB002, in the rat monocrotaline and pneumonectomy model of pulmonary arterial hypertension. *Circulation* 2019;140:A12947.
4. Galkin A, et al. GB002, a novel inhaled PDGFR kinase inhibitor, demonstrates efficacy in the SU5416 hypoxia rat model of PAH. *Circulation* 2019;140: A11102.

ACKNOWLEDGEMENTS

Study 1 was supported in part by NIH grant #HL102946 and sponsored by Pulmokine, Inc.
Study 2 was supported by GB002, Inc., a wholly owned subsidiary of Gossamer Bio, Inc.

DISCLOSURES

JL, MY, MC, RM, RA, and LZ are employees of Gossamer Bio, Inc.

Prepared for presentation at the American Thoracic Society International Conference, May 15-20, 2020 (canceled due to COVID-19). Virtual meeting, August 5-10, 2020. Abstract 2907.